ePO45

Papillary renal cell carcinoma, glioma and colon polyps in a patient with novel *POT1* variant

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Background: *POT1* tumor predisposition (*POT1*-TPD) is a rare autosomal dominant cancer susceptibility syndrome with fewer than 100 families reported in the literature. It is caused by heterozygous pathogenic variants in the *POT1* (protector of telomeres 1) gene. Core cancers associated with *POT1*-TPD include cutaneous melanoma, chronic lymphocytic leukemia (CLL), glioma and cardiac angiosarcoma. Limited evidence suggests that other associated cancers may include colorectal, thyroid and breast angiosarcomas. Less than 100 families have been identified with POT1-TPD to date.
POT1 is part of the telomere shelterin complex which facilitates telomere protection and access. The majority of variants identified in this gene are classified as of uncertain significance due to insufficient data based on ACMG classification criteria.
Case presentation: We present a 56 year old woman with history of chronic left back pain. CT imaging showed a heterogeneously enhancing left renal mass concerning for malignancy. The patient underwent a radical nephrectomy and was diagnosed with papillary renal cell carcinoma (RCC), type 2. She reported a strong, but limited family history of cancer including a brother with lymphoma, mother and maternal aunt with melanoma, father who developed lung cancer and had history of smoking and multiple maternal and paternal relatives with cancer diagnoses of unknown primary. A multi-gene cancer panel revealed a heterozygous likely pathogenic variant in *POT1* (NM_015450.3(POT1):c.125-2A>G). She had a recent colonoscopy which was significant for 8 colon polyps (6 hyperplastic, 2 tubular adenomas) and underwent polypectomy. Follow up brain MRI was ordered based on *POT1*-associated cancer risks. This revealed a left orbitofrontal lesion with findings suggestive of primary glial neoplasm. The patient underwent craniotomy and was diagnosed with a grade 2 glioma with future plans to treat with radiation therapy and systemic chemotherapy. Due to the *POT1*-TDP-related cancer, family history of related cancer, and likely pathogenic variant, the patient was diagnosed with *POT1*-TDP.
The patient has past medical history of headache and obesity. She has a 15 year history of tobacco use with smoking a half pack of cigarettes per day which was discontinued 10 years prior to her presenting for medical attention. She reports moderate alcohol consumption with 4 to 5 drinks per week.
Conclusion: This is to our knowledge, the first reported case of papillary RCC in a person with *POT1*-TPD. *POT1*-TPD has a clear association with cutaneous melanoma, glioma and angiosarcoma. There are patients described with family history of renal cancer; however, those family members did not have genetic testing so it is unknown if they have the *POT1* familial variant. Interestingly, *POT1* is functionally expressed in human embryonic kidney, making it plausible that it increases risk for kidney cancer. While the patient has some risk factors for RCC, we cannot exclude the possibility that the RCC is associated with her diagnosis of *POT1*-TDP. Due to the rarity of *POT1*-TPD it is unclear if additional cancers outside of the core-described cancers are associated with this gene. Further studies are needed to define the *POT1*-TPD tumor spectrum and risks.
The *POT1* c.125-2A>G variant has not been reported in the literature and is not present in population databases. It is classified by the performing laboratory as likely pathogenic. This variant affects an acceptor splice site in intron 6 of the *POT1* gene and is predicted to result in aberrant RNA splicing. Description of this variant in a patient with a core cancer diagnosis (and with family history of core cancer diagnoses) supports the classification as likely pathogenic and may assist in the interpretation of future sequencing results.

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ePO47

Germline cancer predisposition variants in a cohort of early-onset Merkel cell carcinoma patients

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Introduction: Merkel cell carcinoma (MCC) is a rare and highly aggressive skin cancer that is associated with advanced age and immunosuppression. Most patients diagnosed with MCC are older than 70 years of age, with incidence below age 50 being rare. To date, no cases of familial MCC have been reported. To identify possible predisposition alleles in a cohort of 37 early-onset MCC patients, ages 18-49 (median age = 45 years, females = 17, males =27), we performed genome sequencing and subsequent clinical-grade analysis. We report findings from this cohort and discuss the benefits of genome sequencing in detecting germline variants in known cancer predisposition and DNA repair genes.
Methods: We performed genome sequencing on peripheral blood DNA from patients diagnosed with MCC prior to age 50. Analysis was carried out using the custom-enhanced analysis tool, SEQR, developed for the NIAID Centralized Sequencing Program. First-tier analysis focused on rare pathogenic and likely pathogenic variants in known cancer predisposition genes. Additionally, we identified rare variants of unknown clinical significance in the same group of genes.
Results: Our analysis identified variants in known cancer predisposition genes in 16/37 (43%) early-onset MCC patients across 14 autosomal genes. Notably, 5/37 (14%) of these patients were heterozygous for previously well-described pathogenic variants in cancer predisposition genes (*ATM* = 2, *BRCA1* = 2, and *BRCA2*). Furthermore, 4/37 (11%) patients had likely pathogenic variants in other known cancer predisposition genes (*FANCA*, *RAD54L*, *SMARCAD1*, and *TP53*). Additionally, 8/37 (22%) patients had very rare (minor allele frequency ≤ 3.5E-05) variants of uncertain clinical significance in cancer predisposition genes (*APC*, *ATM*, *ERCC4*, *FANCA*, *FGFR3*, *PTCH1*, *TSC1*, *WT1*). Genome-based copy number variant (CNV) analysis did not detect any underlying CNVs in *BRCA1* and *BRCA2*.
Conclusion: Our study demonstrates the clinical value of genomic workup in early-onset MCC patients and suggests that heritable cancer predisposition variants can increase the risk for MCC. As 6 (16%) patients carried variants strongly associated with familial cancer syndromes (*ATM*, *BRCA1*, *BRCA2*, and *TP53*), including inherited risk for breast and other malignancies, the genomic sequencing resulted in a high frequency of personal and familial benefit. Genetic counseling and cascade testing are indicated for patients and their families to ascertain the familial risk for inherited cancer predisposition. Further investigation

of the genetic risk of identified variants toward the development of MCC is warranted. Future studies will include similar workup and analysis in older MCC patients to determine the relative contribution of variants in known cancer predisposition genes to more typical presentations of MCC.

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eP048

Identifying cancer predisposition in a series of 1,521 pediatric oncology patients by tumor-only panel-based testing

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Introduction: Tumor-only profiling by next-generation sequencing (NGS) has been implemented in the pediatric oncology setting to enhance pathologic diagnosis, provide prognosis, and identify molecular targets for therapy. Clinically significant germline variants in cancer susceptibility genes covered by the assay will also be detected with this approach. Current guidelines regarding the threshold of triggering follow-up testing for germline pathogenic variants detected by tumor-only NGS are limited, given the challenge of distinguishing germline vs somatic variants as well as the need for follow-up germline confirmatory testing and genetic consultation. Here, we reviewed the yield and utility of targeted germline testing following tumor DNA sequencing in a diverse pediatric patient population at Children's Hospital Los Angeles.
Methods: We retrospectively analyzed a cohort of 1,521 consecutive patients receiving tumor-only OncoKids cancer panel testing, a comprehensive DNA- and RNA-based NGS assay. For each patient, clinical, pathology, and molecular results were discussed at a weekly or biweekly multidisciplinary tumor board. Recommendations for germline testing were made based on clinical and family history, and one of the following criteria: 1) presence of a Tier I or Tier II variant in a tumor-suppressor gene at a VAF of approximately 50% with no copy number variants or loss of heterozygosity (LOH) in the variant locus; 2) a Tier I or Tier II variant in a tumor-suppressor gene with LOH encompassing the locus in the tumor; 3) the presence of 2 Tier I or Tier II variants in a cancer predisposition gene in the tumor; 4) a Tier I or Tier II variant in the tumor sample that had previously been published in the literature in the germline setting; 5) Tier I or Tier II variant in a cancer predisposition gene for patients with a clinical or family history suggestive of a cancer predisposition syndrome. Targeted Sanger sequencing of a germline sample was performed for the variant(s) detected by the somatic cancer panel. Patients who underwent germline testing using a custom cancer predisposition panel, focused exome analysis, or single-gene testing (eg, *SMARCB1*, *RB1* and *TP53* for patients with rhabdoid tumor, retinoblastoma or Li-Fraumeni syndrome, respectively) were not included in this study.
Results: A total of 1,521 pediatric oncology patients, including 568 with hematological malignancies, 557 with soft tissue and bone tumors, and 396 with CNS tumors, received tumor-only OncoKids testing. Recommendations for targeted germline testing were made for 179 patients (12%) based on the somatic testing results in conjunction with clinical and/or family history. Of these, 102 patients underwent targeted germline testing for the variants detected by tumor sequencing. Germline pathogenic/likely pathogenic variants were identified in 38% (39/102) of patients tested: *TP53* (n=11), *NF1* (n=6), *WT1* (n=5), *DICER1* (n=4), *SMARCB1* (n=3), *PTEN* (n=2), *RET* (n=2), *CBL* (n=2), *KRAS* (n=1), *GATA2* and *MSH6* (n=1), *SMARCA4* (n=1), and *RASA1* (n=1). Three patients showed low-level mosaicism for a *KRAS*, *SMARCB1* or *PTEN* pathogenic variant in the peripheral blood sample. The remaining 63% (64/102) of patients were negative for the variants identified with tumor profiling. Of the 77 patients who did not undergo targeted germline testing, 14 (16%) had a clinical or family history highly suggestive of cancer predisposition. Examples included a patient with a hyper-mutated high-grade glioma suggestive of a mismatch repair disorder, a patient with clear-cell meningioma and LOH encompassing *SMARCE1*, two hemangioblastoma patients, one with a clinical diagnosis of Von Hippel-Lindau syndrome and the other with a loss of chromosome 3p that included *VHL*, and a child with choroid plexus carcinoma and likely germline *TP53* variant.
Conclusion: Targeted germline analysis for variants detected by tumor sequencing increases the percentage of pediatric patients diagnosed with cancer susceptibility which may impact therapy selection, clinical surveillance, and genetic counseling in families. The number of patients with germline susceptibility to cancer is underestimated in this study since 1) not all genes related to cancer susceptibility are included in the somatic panel, eg, *SMARCE1*, 2) due to technical limitations exon level copy number variants and/or complex structural variants may not be detected, and 3) germline testing is not performed for all patients in whom suspected germline pathogenic variant(s) are identified by tumor-sequencing. Both targeted germline follow-up testing and expanded germline analysis independent of tumor sequencing in appropriate patients are needed to comprehensively identify clinically significant germline variants in the pediatric population.

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eP049

Discordant fluorescence in situ hybridization and RNASeq results in the identification of fusion partners in recurring translocations in hematological malignancies

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Introduction: Reciprocal chromosomal translocations are implicated in neoplastic transformation in tumors. These can be identified by chromosome analysis, by fluorescence in situ hybridization (FISH) if cryptic, or by RNASeq/next generation sequencing. FISH probes are highly specific and sensitive, and have the advantage of faster turn-around-time, are less expensive, and can be used on a variety of specimen types. Therefore, several of these probes are commercially available, and are incorporated to screen diagnostic specimens. However, these probes may yield erroneous identification of fusion partners due to the proximity of genes covered by the FISH probe design. Here, we present two examples of this in hematological malignancies.
Methods: Clinical material, bone marrow (BM) or peripheral blood (PB) was evaluated for hematopathology (morphology, immunohistochemistry, and flow cytometry), cytogenetics (karyotype and FISH) and RNASeq (next generation sequencing) methods using standard protocols.
Results: Patient one is a 62-year-old man was diagnosed with plasma cell myeloma (PCM) after he presented with anemia, hypercalcemia, lytic bone lesions, and 80-90% involvement by CD38+ plasma cells in bone marrow (BM). Chromosome analysis of the BM aspirate showed a highly complex karyotype with multiple related clones. FISH analysis with probes for *FGFR3*, *MYC*, *CCND1*, *IGH*, *MAF* and *MAFB* detected *FGFR3* / *IGH* fusion. Therefore, a chromosomal